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The Impact of Rural Residency on the Expression and Outcome of Systemic Lupus Erythematosus: Data From a Multiethnic Latin American Cohort

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Abstract

Objective—To examine the role of place of residency in the expression and outcomes of SLE in a multi-ethnic Latin American cohort.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting or revising this article critically for important intellectual content, and all authors approved the final version to be published. Dr. Bernardo A. Pons-Estel had full access to all of the data from the study and takes responsibility for their integrity and the accuracy of the analyses performed

Patients and Methods—SLE patients (<2 years of diagnosis) from 34 centers constitute this cohort. Residency was dichotomized into rural and urban, cut-off: 10,000 inhabitants. Socio-demographic, clinical/laboratory, and mortality rates were compared between them using descriptive tests. The influence of place of residency on disease activity at diagnosis and renal disease was examined by multivariable regression analyses.

Results—122 (8.6%) of 1426 patients were rural residents. Their median age (onset, diagnosis) were 23.5 and 25.5 years; 85 (69.7%) patients were Mestizos, 28 (22.9%) Caucasians and 9 (7.4%) African-Latin Americans. Rural residents were more frequently younger at diagnosis, Mestizo and uninsured; they also had fewer years of education and a lower socioeconomic status, exhibited hypertension and renal disease more frequently, and had higher levels of disease activity at diagnosis; they used methotrexate, cyclophosphamide pulses, and hemodialysis more frequently than urban patients. Disease activity over time, renal damage, overall damage and the proportion of deceased patients were comparable in both, rural and urban patients.. In multivariable analyses, rural residency was associated with high levels of disease activity at diagnosis (OR 1.65, 95% CI 1.06–2.57) and renal disease occurrence (OR 1.77, 95% CI 1.00–3.11).

Conclusions—Rural residency associates with Mestizo ethnicity, lower socioeconomic status, and renal disease occurrence. It also plays a role on disease activity at diagnosis and kidney involvement but not on the other end-points examined.

INTRODUCTION

A number of population-based studies of systemic lupus erythematosus (SLE) has helped defining the influence of ethnicity and other personal and social characteristics on the clinical expression and outcome of this disease (1–4). However, the influence of place of residence, i.e.: rural vs. urban has only been infrequently addressed and mostly in Caucasian populations. Major findings from these studies reveal the association of increased age at diagnosis, lower female to male ratio around 5:1 compared to typical 9:1 but similar clinical features regarding disease severity and mortality in patients from rural settings as compared to those from urban areas (5, 6). In addition, some data suggest that rural populations experience poorer clinical outcomes probably related to their low socioeconomic status and educational levels and inadequate access to health care (7, 8).

A major disadvantage for SLE patients living in rural areas is the limited availability of providers with adequate levels of expertise to care for them appropriately. It is well documented that SLE mortality is lower in large referral hospitals with experience in treating these patients and that end-stage renal disease in SLE occurs more frequently in populations with limited hospital access (9–11).

Today the boundaries between rural and urban residential areas in developed countries have been affected by globalization, which brings improvements in communication and transportation systems. In Latin America, like in other parts of the world, however, there are still highly distinct geographical areas where the differences between rural and urban settings are quite noticeable. We hypothesized that lupus patients living in rural areas will experience less favorable disease outcomes due not only to a more severe disease but to the modulating effects of poverty, limited health care access and possibly some environmental factors. We have examined such hypothesis using data from a large multi-ethnic Latin American lupus cohort (GLADEL).

PATIENTS AND METHODS

Patients

Patients were those participating in GLADEL (*Grupo Latino Americano De Estudio del Lupus* or Latin American Group for the Study of Lupus), a multinational, inception longitudinal cohort study constituted by Latin American centers having experience in the diagnosis and management of SLE and aimed at determining the different socioeconomic–demographic, clinical, genetic and treatment characteristics in the course and outcome of SLE patients from the region [mestizos (mixed Caucasian and Amerindian ancestry), Caucasians and African-Latin American].

As previously described (12), the GLADEL cohort comprises 34 centers distributed among nine Latin American countries, following each one a common protocol with consensus definitions and outcome measures. Institutional review boards' local regulations were followed at all centers. All data were collected into the ARTHROS database (a user-friendly database developed by Argentinean rheumatologists using a Windows platform, Visual Basic language and Microsoft Access). Data were submitted via Internet to the coordinating center where they were reviewed to ensure their quality.

For all patients the diagnosis of SLE was made by a rheumatologist or a qualified internist with experience in SLE based on the clinical and laboratory features present. Fulfillment of four American College of Rheumatology (ACR) SLE criteria (13, 14) at the time of diagnosis was not mandatory. For this cohort all clinical (related and un-related to SLE), laboratory and therapeutic features were evaluated at disease onset of and during its course (cumulative incidence). Socioeconomic status was defined as per the Graffar scale that takes into account the following five variables: parent's occupation, parent's level of education, main source of income, housing, and neighborhood quality (15). Autoantibodies and complement tests were performed with cutoff values considered to be valid at each center. The activity index (SLEDAI, Systemic Lupus Erythematosus Disease Activity Index) (16) was assessed at the time of entry and then twice a year whereas the damage index (SLICC/ACR or SDI, Systemic Lupus International Collaborating Clinics/ACR Damage Index) (17) was ascertained at entry and yearly thereafter. Exposure to medications was dichotomized according to their use (users and non-users).

The variable of interest, place of residency was dichotomized into rural (<10,000 inhabitants) and urban (≥10,000 inhabitants). End-points were renal disease occurrence, disease activity (diagnosis and over time), renal damage and damage overall, and mortality; renal disease was defined by the respective ACR renal criterion (persistent proteinuria and/or cellular casts, high disease activity was defined as a SLEDAI >11; renal damage and damage overall were defined as per the SDI/ACR index.

Statistical analyses

All variables described above were examined as a function of the place of residency using descriptive statistical tests, Wilcoxon's, Chi-square and Kruskal Wallis tests as appropriate for continuous and categorical variables, respectively. Additionally, multivariable logistic regression models were performed to evaluate the influence of place of residency in disease activity at diagnosis and renal involvement. All results are presented as odds ratios (OR) with their corresponding 95% confidence intervals (CIs). Analyses were performed using either SAS, version 9.1 (SAS Institute, Cary, NC, USA) or SPSS, version 15.0 (Chicago, IL, USA).

RESULTS

One hundred and twenty-two (8.6%) out of 1426 SLE Latin American patients who constitute the GLADEL cohort were identified as living in rural areas. Of them, 107 (87.7%) were women, their median [Q3-Q1 interquartile range] age at disease onset and age at diagnosis were 23.5 [Q3-Q1: 17.0–32.0] and 25.5 [Q3-Q1: 18.0–34.0] years, respectively; their median disease duration 54.2 months [Q3–Q1: 29.9 – 72.9]. Fifty one (41.8%) were without medical insurance, 111 (91.0%) had 12 or less years of formal education and 100 (82.0%) had a low socioeconomic status. Eighty five (69.7%) of the patients living in rural areas were Mestizos, 28 (22.9%) Caucasians and 9 (7.4%) were African-Latin Americans.

Univariable analyses

Table 1 depicts the features of GLADEL SLE patients as a function of place of residency. The proportion of Mestizos was higher among rural patients; conversely there were more Caucasians and African-Latin Americans patients living in urban areas. Rural patients were also younger at diagnosis, while urban patients showed a higher number of years of formal education, better socioeconomic status and medical coverage than those living in rural areas. Within the clinical features, urban patients presented more frequently myalgias/myositis while a comorbid condition such as hypertension and renal disorders were more frequent among patients in the rural areas. Disease activity at diagnosis was significantly higher in rural patients but not over time. Renal damage and overall damage were comparable in both groups. As for the treatment variables the use of methotrexate, cyclophosphamide pulses and the need of hemodialysis were found to be more common in the rural patients. A numerically higher proportion of deaths occurred during follow-up among the rural patients but the difference with the urban patients was not statistically significant. When these features were examined as a function of ethnicity some differences were also observed as noted in Table 2. For example, discoid lupus and pericarditis were more frequent among the African-Latin Americans, while hematological and renal manifestations were more common among both, Mestizo and African-Latin American patients in comparison to the Caucasian patients. Disease activity at diagnosis was also higher in these patients' groups in whom a higher proportion had acquired some renal damage and overall damage. Finally, the use of medications was not uniform across the groups; for example, African-Latin American tended to use higher corticosteroid doses than patients in the other two groups while a higher proportion of non-Caucasians had received pulses of cyclophosphamide and a higher proportion of mestizos had received methotrexate.

Impact of place of residence on disease activity and renal disease

After adjusting for possible confounding factors using multivariable logistic regression models we found that rural residency was statistically associated with high disease activity (SLEDAI>11) at diagnosis (OR 1.65, 95% CI 1.06–2.57) and with the occurrence of renal disease over time (OR 1.77, 95% CI 1.00–3.11) as shown on Tables 3 and 4, respectively.

DISCUSSION

In this study, we have examined the role of place of residency on the expression and outcome of SLE in the largest multi-national Latin American cohort: GLADEL. Patients residing in rural areas were more likely to be Mestizo, to have lower socioeconomic status, educational level and medical insurance coverage and to experience more active disease at diagnosis, renal disease occurrence over time (not previously reported) but not worse outcomes in terms of disease activity over time, renal damage, overall damage and mortality. Socioeconomic factors have been recognized as important mediators of less favorable outcomes in patients from GLADEL (12) as well as in patients studied by others

(18–20) suggesting that, in fact, these factors may play a more important role than place of residency *per se* in terms of their impact on the intermediate (disease activity, renal and overall damage) and final outcomes (mortality) of this disease. However, even after adjusting for the socioeconomic parameters examined, place of residency had an important impact on terms of disease activity at diagnosis and the occurrence of renal disease over the disease course. These data may reflect the fact that rural residents in Latin America may not have the same access to specialized care, being more frequently cared by family or primary physicians, nurse practitioners and physician assistants; in addition, social services may be less available to these patients; the end result is that they may present to the rheumatologists only when the disease is quite evident and active. This has been clearly shown by Ward who found that SLE patients with limited access to care, perhaps a subrogate variable for place of residency, were more likely to develop end stage renal disease (21); however, we could not demonstrate that patients in the rural areas experienced a significant lag time in presenting to a health-care provider as compared to those living in urban settings.

Place of residency may also reflect environmental exposures that may trigger or influence different patterns of disease expression in SLE. While factors such as work-related increase in the levels of sunlight (22, 23), pesticides, herbicides and other exposures (23, 24) are more likely to occur in rural areas of Latin-American, others, like air pollutant levels (25), may be found more frequently in urban areas. Finally, other factors such as smoking (23, 26), higher rates of infections highly associated with lupus such as Epstein Barr virus (27, 28) and rubella (29) may be observed equally in urban and rural areas. Given the fact that our cohort includes patients from different geographic areas and ecological systems of Latin America, it is hard to hypothesize that a single possible exposure could have triggered the onset of this disease or the occurrence of renal disease among rural residents. We must note, however, that environmental exposures were not explored in our study.

The fact that we did not find differences in the rates of hospitalization, and on intermediate (disease activity over the disease course, renal damage and damage overall) and long-term outcomes (mortality) may actually reflect the fact that once patients enter the health system, their course is somewhat comparable to the one of those patients living in urban areas. This is a likely explanation for patients in the GLADEL cohort given that once they are diagnosed they are followed and treated by either rheumatologists or internists with a great degree of experience in the management of SLE. In addition, it is possible that after their enrollment into the cohort these patients may have become proactive in their care, seeking help when their disease was active which may have resulted in avoidable hospitalizations as hypothesized by Ward (30).

The clear strengths of our study include the large number of patients studied, the multiethnic and multinational composition of the cohort including patients living in rural places all around Latin America. From this vantage point, we have dealt with the effect of a variable infrequently assessed in other studies. The primary limitation of our study is that we were unable to include in our analyses data on environmental exposures and access to care (time to appointment and travel distance) since this information had not been obtained; however, place of residency may be a surrogate measure for these later variables in multivariable models.

This study offers a clear picture of the significant socioeconomic-demographic, clinical, serologic and treatment differences present in SLE patients living in urban and rural settings in Latin America. The data presented are important if the care of SLE patients living in rural areas is to improve; thus, it behooves us to keep health authorities in our respective countries informed of our findings so adequate remedial strategies be implemented. Likewise, physicians working in rural areas (commonly primary care physicians) should be aware of

this condition and make every effort to identify patients afflicted with it early enough so that they can be promptly referred to specialists not only for confirmation of their diagnosis but for the implementation of treatment strategies and establishment of an adequate follow up plan.

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APPENDIX A. MEMBERS OF THE GLADEL STUDY GROUP

In addition to the authors, the following individuals are members of the GLADEL Study Group and have incorporated at least 20 patients into the database: from **Argentina**, Luis J. Catoggio, Enrique R. Soriano, María Flavia Ceballos Recalde and Edson Velozo (Medical Clinic Service, Hospital Italiano and Fundación Dr. Pedro M. Catoggio para el Progreso de la Reumatología, Buenos Aires); Jorge A. Manni, Sebastián Grimaudo and Judith Sarano (Instituto de Investigaciones Médicas “Alfredo Lanari,” Buenos Aires); José A. Maldonado-Cocco, María S. Arriola and Graciela Gómez (Instituto de Rehabilitación Psicofísica, Buenos Aires); Mercedes A. García, Ana Inés Marcos and Juan Carlos Marcos (Hospital Interzonal General de Agudos “General San Martín,” La Plata); Hugo R. Scherbarth, Jorge A. López and Estela L. Motta (Hospital Interzonal General de Agudos “Dr. Oscar Alende,” Mar del Plata); Cristina Drenkard, Susana Gamron, Laura Onetti and Sandra Buliubasich (Hospital Nacional de Clínicas, Córdoba); Francisco Caeiro and Alejandro Alvarellos (Hospital Privado, Centro Médico de Córdoba, Córdoba); Silvana Gentiletti, Norberto

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Table 1

Socioeconomic-demographic, cumulative clinical, serologic and treatment characteristics of SLE patients from the GLADEL cohort compared as a function of place of residency *

Variable	Place of Residency		P
	Urban (n=1304)	Rural (n=122)	
Age at diagnosis, years, median	27.0	25.5	**0.0442**
Delay in diagnosis (days), median	179	202	0.3112
Female, %	89.9	87.7	0.4505
Ethnicity, %			
Mestizo (n=638)	42.4	69.7	
Caucasian (n=603)	44.1	22.9	**<0.0001**
African-Latin American (n=185)	13.5	7.4	
Education level, years, %			
0–7 years (n=447)	30.3	42.6	
8–12 years (n=647)	45.1	48.4	**0.0002**
>12 years (n=332)	24.6	9.0	
Lacking medical insurance, %	15.6	41.8	**<0.0001**
Socioeconomic status, %			
Low (n=867)	59.0	82.0	
Middle (n=408)	29.8	16.4	**<0.0001**
High (n=145)	11.2	1.6	
Hypertension, %	37.0	46.7	**0.0350**
Myalgia/myositis, %	23.9	16.4	0.0598
ACR Criteria, %			
Malar rash	64.5	70.0	0.2517
Discoid lupus	13.3	13.9	0.7977
Photosensitivity	58.9	61.5	0.5794
Oral ulcers	44.2	49.2	0.2872
Arthritis/arthralgias	92.2	91.8	0.8831
Pleuritis	24.9	26.2	0.7501
Pericarditis	17.6	18.0	0.8960
Psychosis/seizures	14.0	15.6	0.6236
Hematological disorder	78.1	84.4	0.1014
Renal disease	50.8	65.6	**0.0017**
Antinuclear antibodies, %	97.9	99.2	0.7236
Anti-dsDNA antibodies, %	73.4	66.3	0.3029
aPL § antibodies, %	56.7	53.3	0.6094
SLEDAI † at diagnosis, median	10	13	**0.0067**
SLEDAI † during follow-up, median	3.3	4.0	0.6063
SDI ‡ >1, %	78.6	63.1	0.2174
Renal damage ‡ during follow-up, %	25.2	25.4	0.9651

Variable	Place of Residency		P
	Urban (n=1304)	Rural (n=122)	
Medications, %			
Antimalarials	81.9	91.2	0.8196
Methotrexate	11.1	18.9	**0.0113**
Cyclophosphamide pulses	34.1	43.4	**0.0390**
Glucocorticoids (doses)¶			
< 7.5 mg	1.8	1.6	0.9426
7.5mg-15mg	11.9	11.5	
>15mg-<60mg	43.1	46.7	
≥60mg	37.1	33.6	
Hemodialysis, %	4.1	9.0	**0.0115**
Death during follow-up, %	5.7	8.2	0.2579

*SLE = systemic lupus erythematosus; GLADEL = (Grupo Latino Americano De Estudio de Lupus); ACR=American College of Rheumatology.

†SLEDAI=Systemic Lupus Erythematosus Disease Activity Index.

‡SLICC (Systemic Lupus International Collaborating Clinics) Damage Index.

§Antiphospholipid antibodies.

¶As prednisone dose or equivalent.

Table 2

Socioeconomic-demographic, cumulative clinical, serologic and treatment characteristics of SLE patients from the GLADEL cohort compared as a function of ethnicity *

Variable	Ethnicity			P value
	Caucasian (n=603)	Mestizo (n=638)	ALA (n=185)	
Age at diagnosis, years, median	28.0	27.0	25.0	**0.0106**
Delay in diagnosis (days), median	186.0	199.0	123.0	**0.0003**
Female, %	91.0	88.2	90.3	0.2584
Education level, years, %				
0–7 years (n=447)	32.7	27.3	41.1	
8–12 years (n=647)	40.8	51.9	37.8	**<0.0001**
>12 years (n=332)	26.5	20.9	21.1	
Lacking medical insurance, %	16.8	18.2	15.2	0.5881
Socioeconomic status, %				
Low (n=867)	52.0	64.2	78.9	
Middle (n=408)	33.3	28.7	13.5	**<0.0001**
High (n=145)	14.7	7.1	7.6	
Hypertension, %	32.0	41.4	44.9	**0.0003**
Myalgia/myositis, %	23.9	24.5	17.3	0.1154
ACR Criteria, %				
Malar rash	66.3	65.1	60.0	0.2863
Discoid lupus	13.3	11.3	19.5	**0.0152**
Photosensitivity	62.0	56.3	59.5	0.1190
Oral ulcers	43.3	47.2	40.0	0.1553
Arthritis/arthralgias	92.5	91.9	91.9	0.8951
Pleuritis	26.4	23.5	26.0	0.4862
Pericarditis	17.1	15.7	26.0	**0.0049**
Psychosis/seizures	12.9	16.1	10.8	0.1038
Hematological disorder	74.8	80.4	84.9	**0.0046**
Renal disease	44.0	58.5	56.2	**<0.0001**
Antinuclear antibodies, %	99.5	96.3	98.9	**0.0002**
Anti-dsDNA antibodies, %	69.5	77.1	71.0	**0.0192**
aPL § antibodies, %	58.1	58.1	46.0	0.0547
SLEDAI † at diagnosis, median	10.0	11.0	13.0	**0.0003**
SLEDAI † during follow-up, median	3.3	3.6	3.6	0.3290
SDI ≠ >1 %	63.5	72.4	68.1	**0.0035**
Renal damage ‡ during follow-up, %	19.6	29.6	28.7	**0.0001**
Medications, %				
Antimalarials	82.3	80.6	85.4	0.3083
Methotrexate	8.5	15.5	9.7	**0.0004**
Cyclophosphamide pulses	29.7	38.7	38.9	**0.0018**

Variable	Ethnicity			P value
	Caucasian (n=603)	Mestizo (n=638)	ALA (n=185)	
Glucocorticoids (doses)[¶]				
< 7.5 mg	2.7	1.1	1.1	
7.5mg-15mg	13.3	12.1	6.5	**0.0415**
> 15mg-<60mg	40.5	45.9	44.3	
≥ 60mg	37.1	34.6	43.2	
Hemodialysis, %	3.5	5.2	5.4	0.2890
Death during follow-up, %	6.1	5.6	6.0	0.9337

[*] SLE = systemic lupus erythematosus; GLADEL = (*Grupo Latino Americano De Estudio de Lupus*); ACR=American College of Rheumatology.

[†] SLEDAI=Systemic Lupus Erythematosus Disease Activity Index.

[‡] SLICC (Systemic Lupus International Collaborating Clinics) Damage Index.

[§] Antiphospholipid antibodies.

[¶] As prednisone dose equivalent.

Table 3

Multivariable Logistic Regression Model with SLEDAI > 11 at Diagnosis as an Endpoint in SLE patients from the GLADEL cohort

Model	Variable	OR	95% CI	P
Full	Rural residency	1.55	0.99–2.45	0.0567
Reduced	Rural residency	1.65	1.06–2.57	0.0275

Adjusted for age, gender, ethnicity, insurance, education and socioeconomic status

Table 4

Multivariable Logistic Regression Model with Renal Disease as an Endpoint in SLE patients from the GLADEL cohort

Model	Variable	OR	95% CI	P
Full	Rural residency	1.77	1.00–3.12	0.0487
Reduced	Rural residency	1.77	1.00–3.11	0.0484

Adjusted for age, gender, ethnicity, socioeconomic status, insurance, education, SLEDAI at diagnosis, hypertension, myalgia/myositis, methotrexate, cyclophosphamide pulses and hemodialysis.